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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,377	10/30/2000	Toshikazu Nakamura	Q 61434	7003

7590 10/15/2007

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EXAMINER	
ALLEN, MARIANNE P	
ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
10/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/674,377	NAKAMURA, TOSHIKAZU	
	Examiner	Art Unit	
	Marianne P. Allen	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,6,12-14,16 and 28-37* is/are pending in the application.

4a) Of the above claim(s) *16 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6,12-14 and 28-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,2,4,6,12-14,16 and 28-37* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/3/07 has been entered.

Claims 1-2, 4, 6, 12-14, 16, and 28-37 are pending.

Claims 1-2, 4, 6, 12-14, and 28-36 are under consideration. Claims 16 and 37 remain withdrawn.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Japan on 4/28/1998.

Review of the electronic file shows that a certified copy of this document was submitted on 10/30/2000 and is present in the file.

Claim Objections

Applicant is advised that should claim 12 be found allowable, claim13 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

These claims appear to be identical.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4, 12-14, 28, 30-31, 33-34, and 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims have been substantively amended. No basis for the changes has been pointed to and none is apparent.

For example, SEQ ID NO: 2 does not possess "at least one hairpin domain and four Kringle domains." Applicant's response of 5/3/07 at page 15 specifically states that an intact first Kringle domain is not present in SEQ ID NO: 2. Five amino acids are deleted from this domain.

With respect to claim 4, SEQ ID NO: 1 (having no deletion at amino acids 162-166) cannot be obtained by enzymatic digestion of human HGF "harboring a deletion of amino acids 162-166."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Date et al. (1997).

Date et al. discloses HGF variant HGF/NK4, which is the same molecule as SEQ ID NO: 1 of the instant application. The protein was used to examine the mitogenic activity on rat hepatocytes in primary culture (page 4 and Figure 3). As disclosed in the instant specification, SEQ ID NO: 1 implicitly possesses the hairpin domain and four Kringle domains. (See specification pages 13 and 22.)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Date et al. in view of Nakamura et al. (EP 0461560, 1991).

Claims 1-2 and 4 have not been included in this ground of rejection in view of the new matter rejection above. Should the "at least one hairpin domain and four Kringle domain" limitation be removed, these claims would also be subject to this rejection.

Date et al. discloses HGF variant HGF/NK4, which is the same molecule as SEQ ID NO: 1 of the instant application. The protein was used to examine the mitogenic activity on rat hepatocytes in primary culture (page 4 and Figure 3), and thus would necessarily have been in a pharmaceutically acceptable formulation. The protein was made in CHO cells. At page 31 of

the specification as filed, it is disclosed that the protein, as made by CHO cells, has an N-terminus of Pyr-Glu. Date et al. does not disclose SEQ ID NO: 2.

SEQ ID NO: 2 as recited in claim 6 differs from the disclosure of Date et al. in that SEQ ID NO:2 has a deletion of 5 amino acids relative to the protein of SEQ ID NO: 1.

Nakamura et al., disclose a variant of HGF comprising the same 5 amino acid deletion relative to SEQ ID NO: 1 as found in SEQ ID NO: 2, see Figure 3 and claim 3. They disclose the protein having that 5 amino acid deletion to have HGF activity, and thus to be able to bind to HGF receptors.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make a variant of the protein of Date et al. having the 5 amino acid deletion taught by Nakamura et al. (arriving at a protein having the amino acid sequence of SEQ ID NO: 2), to be used in pharmaceutical compositions as an HGF antagonist, as taught by Date et al. The person of ordinary skill in the art would have been motivated to do so by Nakamura's implicit teachings that the deleted protein was considered to be functionally equivalent to the other form of HGF, and would have expected success for the same reason. Accordingly, the invention, taken as a whole, is *prima facie* obvious.

The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. The skilled artisan would have had reason to try this methodology with the reasonable expectation of success.

Claims 29, 32, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwall et al., U.S. Patent No. 6,207,152 (priority date 2/17/1998) in view of Date et al. and Nakamura et al.

Claims 12-14, 28, 30-31, 33, 34, and 36 have not been included in this ground of rejection in view of the new matter rejection above. Should the "at least one hairpin domain and four Kringle domain" limitation be removed, these claims would also be subject to this rejection.

Schwall et al. teach the treatment of various cancers with HGF antagonist antibodies (see claims). In the detailed description at paragraph 23, they teach:

> The terms "cancer" and "cancerous" when used herein refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma, lymphoma, sarcoma, blastoma and leukemia. More particular examples of such cancers include squamous cell carcinoma, lung cancer (small cell and non-small cell), gastrointestinal cancer, liver cancer, kidney cancer, pancreatic cancer, cervical cancer, bladder cancer. hepatoma, breast cancer, colon carcinoma, and head and neck cancer. While the term "cancer" as used herein is not limited to any one specific form of the disease, it is believed that the methods of the invention will be particularly effective for cancers which are found to be accompanied by increased levels of HGF or overexpression or activation of HGF receptor in the mammal.

Schwall et al. do not teach a method in which a derivative of HGF is used as the antagonist.

The teachings of Date et al. and Nakamura et al. are summarized above. The combination of these two references renders obvious an HGF antagonist variant or inhibitor

protein having the amino acid sequence of SEQ ID NO: 2. In addition to the above teachings, Date teaches in the introduction that HGF is known in the art to be a pleiotrophic growth factor that targets epithelial and endothelial cells, to be involved in branching tubular morphogenesis, tumor invasion, and to stimulate neovascularization in tumors. Date teaches at page 6 that the protein "may have therapeutic potential to prevent invasion and metastasis of various carcinoma cells." Accordingly, It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the protein found obvious above over Date et al. in view of Nakamura et al. to treat cancer or any other medical condition in which neovascularization is a problem, in view of Schwall's teachings, and would have expected success in view of Date's teachings that the protein (without the 5 aa deletion) is an effective HGF antagonist and Nakamura et al., teaching that the 5 amino acid deletion does not affect binding activity, taken with Schwall's teachings of treating a wide variety of cancers with HGF inhibitors. Accordingly, the invention, taken as a whole, is *prima facie* obvious.

Applicant's arguments regarding sequence discrepancies between SEQ ID NO: 2 and the sequence of Nakamura et al. are not understood. An alignment of these sequences is provided below.

```
AAR15624
ID   AAR15624 standard; protein; 723 AA.
XX
AC   AAR15624;
XX
DT   25-MAR-2003  (revised)
DT   18-MAR-1992  (first entry)
XX
DE   Human leukocyte-derived HGF encoded by clone HLC3.
XX
KW   Hepatocyte growth factor; liver; hepatoma.
XX
OS   Homo sapiens.
XX
PN   EP461560-A.
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XX
PD   18-DEC-1991.
XX
PF   07-JUN-1991;   91EP-00109369.
XX
PR   11-JUN-1990;   90JP-00152474.
XX
PA   (TOYM ) TOYO BOSEKI KK.
XX
PI   Nakamura T,  Hagiya M,  Seki T,  Shimonishi M,  Shimizu S,  Ihara I;
PI   Sakaguchi M,  Asami O;
XX
DR   WPI; 1991-370578/51.
DR   N-PSDB; AAQ15177.
XX
PT   Recombinant human leukocyte-derived hepatocyte growth factor - with DNA
PT   encoding it, recombinant expression vectors and transformant cells
PT   expressing it.
XX
PS   Claim 3; Fig 3; 33pp; English.
XX
CC   The sequence was deduced from a portion of HLC3, one of two clones, (for
CC   HLC2 see AAR15623) isolated from a cDNA library prepd. from mRNA
CC   extracted from human leukocytes. HLC2 has almost the same sequence as
CC   HLC3 except for five residues (162-166) in HLC2 which do not appear in
CC   HLC3. HLC3 shows similar characteristics to the human liver-derived HGF
CC   identified in Nature, 342, 440, 1989, but differs at 14 positions in the
CC   amino acid sequence. The DNA sequence can be expressed and the resulting
CC   protein, recombinant HGF, used in hepa- tocyte cultivation, liver
CC   regeneration, hepatocyte research, esp. into the mechanism of hepatoma,
CC   and to prepare anti-HGF antibodies for diagnosis and therapy. (Updated on
CC   25-MAR-2003 to correct PI field.)
XX
SQ   Sequence 723 AA;

  Query Match             99.9%;  Score 2576;  DB 2;  Length 723;
  Best Local Similarity   99.8%;  Pred. No. 1.9e-163;
  Matches  441;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 ERKRRNTIHEFKKSAKTTLIKIDPALKIKTKKVNTADQCANRCTRNKGLPFTCKAFVFDK 60
              :||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         32 QRKRRNTIHEFKKSAKTTLIKIDPALKIKTKKVNTADQCANRCTRNKGLPFTCKAFVFDK 91

Qy         61 ARKQCLWFPFNSMSSGVKKEFGHEFDLYENKDYIRNCIIGKGRSYKGTVSITKSGIKCQP 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         92 ARKQCLWFPFNSMSSGVKKEFGHEFDLYENKDYIRNCIIGKGRSYKGTVSITKSGIKCQP 151

Qy        121 WSSMIPHEHSYRGKDLQENYCRNPRGEEGGPWCFTSNPEVRYEVCDIPQCSEVECMTCNG 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        152 WSSMIPHEHSYRGKDLQENYCRNPRGEEGGPWCFTSNPEVRYEVCDIPQCSEVECMTCNG 211

Qy        181 ESYRGLMDHTESGKICQRWDHQTPHRHKFLPERYPDKGFDDNYCRNPDGQPRPWCYTLDP 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        212 ESYRGLMDHTESGKICQRWDHQTPHRHKFLPERYPDKGFDDNYCRNPDGQPRPWCYTLDP 271

Qy        241 HTRWEYCAIKTCADNTMNDTDVPLETTECIQGQGEGYRGTVNTIWNGIPCQRWDSQYPHE 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        272 HTRWEYCAIKTCADNTMNDTDVPLETTECIQGQGEGYRGTVNTIWNGIPCQRWDSQYPHE 331

Qy        301 HDMTPENFKCKDLRENYCRNPDGSESPWCFTTDPNIRVGYCSQIPNCDMSHGQDCYRGNG 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        332 HDMTPENFKCKDLRENYCRNPDGSESPWCFTTDPNIRVGYCSQIPNCDMSHGQDCYRGNG 391

Qy        361 KNYMGNLSQTRSGLTCSMWDKNMEDLHRHIFWEPDASKLNENYCRNPDDDAHGPWCYTGN 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        392 KNYMGNLSQTRSGLTCSMWDKNMEDLHRHIFWEPDASKLNENYCRNPDDDAHGPWCYTGN 451
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Qy        421 PLIPWDYCPISRCEGDTTPTIV 442
              ||||||||||||||||||||||
Db        452 PLIPWDYCPISRCEGDTTPTIV 473
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Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 571-272-0712. The examiner can normally be reached on Monday-Friday, 5:30 am - 2:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marianne P. Allen

Primary Examiner 10/5/07

Art Unit 1647

mpa